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ART UNIT	PAPER NUMBER
1641	

NOTIFICATION DATE	DELIVERY MODE
06/11/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@mwzb.com

Office Action Summary	Application No.	Applicant(s)	
	10/551,298	BERGMANN ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11, 13-14, 16, 18-70* is/are pending in the application.

4a) Of the above claim(s) *13,14,18 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-11,16,19-29 and 31-70* is/are rejected.

7)☒ Claim(s) *2,10,19,35 and 43* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 July 2009* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/9/2009, 8/12/2009, 2/25/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of **prognosis of disease** in the reply filed on 2/25/2010 is acknowledged. The traversal is on the ground(s) that the examiner has not established that an undue searching burden would be required in searching methods of prognosis together with methods of diagnosis and of therapy-accompanying monitoring (Reply, page 1).

2. This is not found persuasive because the search for methods of prognosis would not necessarily uncover art teaching diagnosis or therapy-accompanying monitoring. It is typical to find publications that report a single clinical study that focuses on a single outcome, e.g. either diagnosis or prognosis. Consequently, the searches for the various clinical goals are non-coextensive. In addition, each of these clinical goals requires a separate analysis for patentability under 35 U.S.C. 112, 1st paragraph. For all of these reasons, it is maintained that it would be burdensome to search and examine all species.

3. However, since the species of diagnosis was previously searched, both **diagnosis** and **prognosis** of disease will be examined below.

The requirement is still deemed proper and is therefore made FINAL.

4. Claims 16 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2/25/2010.

5. The claims are also subject to examination in light of the elected species of **cardiac disease**. In the instant Reply, Applicant also requests rejoinder of the species of sepsis and

cancer, on the basis that a search of these species would not impose undue burden (Reply, see paragraph bridging pages 22-23).

This is not found persuasive because such arguments are untimely. Applicant's response to this election of species requirement was made **without traverse** on 1/2/2008 (see also the Office action mailed 3/27/2008 at page 1).

Notwithstanding the above, the searches for the disparate diseases are non-coextensive and would require the use of different search terms in searching the patent and non-patent literature. Furthermore, the different species are likely to raise different non-art issues, in that patentability under 35 U.S.C. 112, 1st paragraph must be separately analyzed and assessed for each disease.

Status of the Claims

6. Claims 12, 15, and 17 were canceled. New claims 33-70 have been added. Claims 13-14, 18, and 30 are withdrawn. Accordingly, claims 1-11, 13-14, 16, and 18-70 are pending in the application. Claims 1-11, 16, 19-29, and 31-70 are subject to examination below in light of the elected specie of **diagnosis** or **prognosis** of **cardiac disease**.

Terminal Disclaimer

7. The terminal disclaimer filed on 7/9/2009 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. 7,547,553 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Objections/ Rejections Withdrawn

8. The objections to the specification and claims set forth in the previous Office action have been withdrawn in response to Applicant's amendments thereto.

9. The rejections under § 112, 1st paragraph not reiterated below have been withdrawn in view of Applicant's amendments.

10. The rejections under § 102 and § 103 over Bougueleret et al. not reiterated below have been withdrawn in response to Applicant's amendments to the claims, such that some of the claims are now entitled to the benefit of a prior-filed application.

11. The obviousness-type double patenting rejections over Application No. 11/997250 (now 7,547,553) have been withdrawn in view of Applicant's filing of the above-mentioned terminal disclaimer.

Specification

12. The amendment filed 7/9/2009 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

13. The amendments to the paragraph bridging pages 6-7 are as follows:

> Applicant carried out an exploratory experiment on the detection of pro-adrenomedullin in sera of sepsis patients using a commercially available RIA with an antibody which binds to the amino acids 45-92 of ~~pre-~~pro-AM but not to sequences of mature AM.

Applicant has therefore changed "pre-proAM" to "pro-AM". Basis for this amendment, which changes the scope of the disclosure as originally filed, is not apparent.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Objections

14. Claims 2, 10, 19, 35, and 43 are objected to because of the following informalities:

15. Claim 2 recites "said antibodies which specifically recognize a sequence of mid-proAM" in line 3. This reference to antibodies in the *plural* presents confusion, because claim 1 refers to "a monoclonal or polyclonal antibody", i.e. to a *single* antibody which may be either monoclonal or polyclonal in nature. Clarification is requested as to what is meant by "said antibodies". For the purposes of examination, it was presumed that claim 2 is directed to a method wherein the antibody of claim 1 is labeled.

16. In addition, the recitation of "said antibodies which specifically recognize a sequence of mid-proAM" in claim 2 is confusing because the independent claim does not introduce the antibody as specifically recognizing a sequence of mid-proAM. Rather, claim 1 only indicates that the antibody is specific to the mid-regional partial peptide. If Applicant intends claim 2 to refer back to the same antibody that is mentioned in claim 1, it is suggested that consistent terminology be used when referring to the antibody.

17. Claim 10 refers to "the first and the second antibodies". Although claim 3 invokes a "labeled antibody" and "at least one additional antibody", these antibodies are not described using the terms "first" and "second", such that the reference in claim 10 to "the first and the

second antibodies" may present confusion. Applicant is requested to employ consistent terminology throughout the claims when referring to the antibodies.

18. Claim 19 concludes with the recitation of "said partial peptide sequence". The claim earlier refers to "the mid-regional partial peptide of proadrenomedullin (mid-proAM) but does not specifically mention a "sequence". To avoid confusion, Applicant is requested to employ consistent terminology throughout the claims.

19. Claim 35 recites "an antibody specific to said mid-proAM which consists of the sequence of SEQ ID NO:3". It appears that Applicant intends that mid-proAM consists of the sequence of SEQ ID NO:3. As written, however, the claim may be misread as meaning that the *antibody* consists of SEQ ID NO:3. Applicant is requested to amend the claim for clarity.

20. Claim 43, the last line, "mi-proAM" should apparently read --mid-proAM--.

Claim Rejections - 35 USC § 112

21. Claims 23, 32-34, 38, and 43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

22. Claim 23, added by amendment on 9/28/2008, recites that "said measured level has an order of magnitude of 12 times said level in a healthy person". Similarly, newly added claims 34 and 38 also recite that "said level measured has an order of magnitude of 12 times said level in a healthy person".

The specification discloses "literature data which report increased [adrenomedullin] values of the order of magnitude of 12 times the normal value in the case of sepsis" (specification, page 6, lines 25-27).

However, this discussion of prior art fails to provide support for the newly claimed subject matter. In particular, the noted passage discusses measurement of adrenomedullin, while the instant claims relate to methods of measuring a distinct peptide, mid-proAM.

In addition, the discussion of prior art relates to the level of AM in sepsis patients. Instant claims 23 and 34 are not limited in this manner, but encompass methods of obtaining the recited fold-increase levels of mid-proAM in any patient population.

23. Claim 32, as amended in the instant Reply, now recites that measurement of SEQ ID NO:3 is conducted "using an immunoassay which does not employ an antibody against the partial peptide 66-113 of preproadrenomedullin".

Applicant's Reply indicates support for this negative limitation at page 6, lines 16-18 (Reply, paragraph bridging pages 24-25). It appears that Applicant is referring to the specification as it has been amended in the instant Reply, which has been objected to above as introducing new matter. Applicant also refers to arguments made in a previous response. However, support for the noted limitation is not found in the specification or claims as originally filed. In addition, it is unclear how arguments made by counsel postfiling can form the basis for newly added claim limitations.

MPEP 2173.05(i) states:

> Any negative limitation or exclusionary proviso must have basis in the original disclosure. If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. See In re Johnson, 558 F.2d 1008, 1019, 194 USPQ 187,196 (CCPA 1977) ("[the] specification, having described the whole, necessarily

> described the part remaining."). See also Ex parte Grasselli, 231 USPQ 393 (Bd. App. 1983), aff 'd mem., 738 F.2d 453 (Fed. Cir. 1984). The mere absence of a positive recitation is not basis for an exclusion. Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

In the instant case, the limitation that the immunoassay does not employ an antibody against the partial peptide 66-113 of preproadrenomedullin is not disclosed in the application as filed. The specification as originally filed does not contain a positive recitation of antibodies against the partial peptide 66-113 of preproadrenomedullin. Therefore, no basis is apparent for excluding methods that use such antibodies.

24. New claim 33 recites a method for the indirect determination of adrenomedullin, comprising measuring mid-proAM. The claim concludes with the recitation that "said mid-proAM level correlating with the level of adrenomedullin". Support for this recitation could not be found in the specification or claims as originally filed. Rather, the specification discusses how fragments of the same precursor peptide, in this case pre-proAM, can differ in concentration (see pages 4-5). As such, neither explicit nor implicit support is apparent for the claimed subject matter.

25. New claim 43 recites an immunoassay using a "specific binding partner for an epitope in said mi-proAM [sic]". The specification does not disclose the term "specific binding partner". The specification discloses art-recognized methods of making *antibodies* specific for mid-proAM. However, the genus of "specific binding partners" is not introduced, nor are any other types of specific binding partners other than antibodies suggested or described. The specification does not disclose any methods of making specific binding partner other than antibodies. With the exception of antibodies, no complete or partial structure of a "specific binding partner" capable

of recognizing the recited epitope is disclosed, e.g. through detailed drawings or through a chemical formula.

Scope of Enablement

26. Claims 16, 24, 26-29, 39, 42, 51, 56, 64, and 59 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods in which mid-proAM is measured, does not reasonably provide enablement for methods in which mid-proAM measurements are used for diagnosis, prognosis, or therapy-accompanying monitoring of a disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The nature of the invention relates to an immunoassay method for measuring the level of mid-proAM. The specification discloses that as compared to healthy subjects, measured levels were higher in patients with sepsis, cardiac diseases, and cancer (see Figure 2 and [0075] of the published application).

The claims at issue recite methods for the diagnosis or prognosis of a disease, wherein the level of mid-proAM (or a peptide that "has" this sequence) is measured. See especially claim 27. When the claims are given their broadest reasonable interpretation, they would encompass methods in which diagnosis is made based on the measured levels of mid-proAM. As such, Applicant is claiming methods in which the measured levels can be used to diagnose, prognose, or monitor <u>any</u> disease.

The data presented in the specification indicate that measurements of mid-proAM were higher in patients with sepsis, cardiac diseases, as well as cancer when compared to healthy controls, suggesting that mid-proAM is not specific to any one disease, but rather is elevated in a number of different diseases.

However, there is no guidance with regard to *differential* diagnosis of disease. Rather, all of the examples in the specification relate to subjects whose disease condition was already known, i.e., those subjects who were already diagnosed with the disease. As a result, one skilled in the art would not know, upon observing elevated mid-proAM levels in an unknown subject, whether to diagnose a subject with sepsis, a cardiac disease, a cancer, or some other disease.

A large number of cardiac disorders are known in the art, which may differ substantially in etiology, pathology, and course of disease. See for example Merck Manuals Online Medial Library (section index for "Heart and Blood Vessel Disorders"; Home Edition, retrieved from www.merck.com/mmhe on 3/29/08), which teaches that disorders of the heart include abnormal heart rhythms such as atrial fibrillation; aneurysms; atherosclerosis; cardiomyopathy; pericarditis; and cancerous tumors of the heart.

The specification does not provide details regarding the patient population studied (see Figure 2), such that it cannot be determined which of the many known cardiac diseases mid-proAM might be correlated with.

With respect to *prognosis* of disease, there are no working examples in which levels of mid-proAM were correlated with prognosis of any disease. For example, there are no data provide to show that mid-proAM levels differ to a statistically significant degree among subjects who later died of their disease vs. those who survived. The specification is devoid of any data

that would correlate altered levels of mid-proAM with any disease state, and therefore fails to provide guidance with regard to how to use mid-proAM levels for prognosis of any disease.

Consequently, further experimentation would be necessary in order to first determine whether mid-proAM measurements could in fact be used for diagnosis or prognosis, i.e. whether levels might be correlated with disease and/or indicative of future morbidity or mortality. This would mean conducting large-scale clinical trials in order to compare the levels in both control and disease patients, and to determine whether statistically significant changes are observed. Since Applicant is broadly claiming diagnosis and prognosis of all diseases (except sepsis), such studies would need to be conducted for each disease.

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

In the instant case, Applicant has argued that mid-proAM is a "newly discovered partial peptide" which was "heretofore not known" (Reply of 10/7/2009 at page 21). Similarly, Applicant has argued that "[i]t was not heretofore known that the mid-regional partial peptide

even existed in human blood" (see the Reply of 12/30/2008 at page 16, last paragraph). In view of the fact that little was apparently known about the peptide, the limited data presented in the specification do not bear a reasonable correlation to the scope of the claims.

27. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

28. Claims 23, 26-29, 34, and 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

29. Claims 27-29 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a step in which a disease is diagnosed.

Claim 27 recites a method "for the diagnosis of a disease other than sepsis" and concludes with the step of "correlating said level of said mind-regional [sic] partial peptide with the presence of said disease". However, the claim lacks an active method step in which the subject is actually diagnosed with disease.

30. Claims 23, 34, and 38 recite that "said measured level has an order of magnitude of 12 times said level in a healthy person". Applicant's intended meaning is unclear. The reference to "12 times said level in a healthy person" suggests that the measured level is 12 times more than that in a healthy person, i.e. a 12-fold increase. However, the inclusion of the term "an order of magnitude" presents confusion, as it invokes the idea that the measured level is being increased by powers of ten. Clarification is needed as to the scope of the claims.

Claim Rejections - 35 USC § 102

31. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

32. Claims 23, 32-33, 43-44, 52-53, 57, 65-66, and 70 are rejected under 35 U.S.C. 102(e) as being anticipated by Bougueleret et al. (US 2007/0082363 A1, of record).

The claims at issue are not entitled to the benefit of an earlier filing date (see new matter rejection above), such that the Bougueleret et al. reference constitutes prior art under 35 U.S.C. 102(e)

Bougueleret et al. teach diagnosis of cardiovascular disorders by detecting and/or quantifying SEQ ID NO:3 ("CPP 19") and other so-called "cardiovascular disorder plasma polypeptides" or CPPs) (see especially claims 1-5 and paragraphs 12-14, 28, 35, 63-68, 140-161, 168-212). SEQ ID NO:3 as taught by Bougueleret et al. is identical to instant SEQ ID NO:3 (see Figure 1 of the reference and the Examiner's sequence search results via SCORE). Quantification may be via sandwich or "double determinant" ELISA assays that use two antibodies, one of which is labeled directly or indirectly (paragraph 177 on page 27).

Bougueleret et al. discuss how the antibodies are preferably "specific" for the CPPs of the invention and do not bind other peptides with high affinity [0168]. Therefore, with respect to

claim 32, it is presumed that the prior art antibodies are not "against" other peptides such as the partial peptide 66-113 of preproadrenomedullin.

With respect to claim 33, the reference teaches assaying SEQ ID NO:3 in plasma (see, e.g., paragraphs 35, 207, and claim 5). The methods of Bougueleret et al. anticipate all active method steps recited in the claim, namely the measurement of SEQ ID NO:3 in a biological fluid. Although the reference does not characterize measurement of SEQ ID NO:3 as being tantamount to "indirect determination of adrenomedullin" or state that the level of SEQ ID NO:3 correlates with the level of adrenomedullin, such statements may be reasonably interpreted as simply reflecting intrinsic physiological properties of SEQ ID NO:3.

With respect to claim 43, Bougueleret et al. teach both polyclonal and monoclonal antibodies (i.e., "specific binding partners"; see [0154], [0157]). Such anti-CPP antibodies may be made by immunizing mammals with the CPP or a fusion protein thereof [0154], [0157], i.e., in this case CPP 19 or SEQ ID NO:3.

With respect to claim 23, it is noted that the claim does not clearly require an active method step in which levels are measured from a sample taken from a patient suffering from sepsis. As such, the claim may be interpreted as a statement regarding inherent properties of the assay; i.e., that when the assay is used for this intended purpose, it would produce a measured value as claimed. Since the assay of Bougueleret et al. is indistinguishable from the claimed assay as detailed above, it is presumed that the prior art assay would also be capable of performing as claimed even though the reference is silent with respect to sepsis.

Claim Rejections - 35 USC § 103

33. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

34. Claims 1-9, 16, 19-22, 24-29, 31-33, 35-37, 39-53, 55-66, and 68-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harlow & Lane (Harlow, E. and Lane, D., Antibodies: A Laboratory Manual (1988) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, pages 53, 60-61, 72-76, 555, 559, 561, and 578-579) in view of Kennedy et al. ("Expression of the Rat Adrenomedullin Receptor or a Putative Human Adrenomedullin Receptor Does Not Correlate with Adrenomedullin Binding or Functional Response" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS 244, 832–837 (1998).

Harlow & Lane teach that to detect and quantitate antigens, the most useful method is the two antibody sandwich assay. This assay employs either two monoclonal antibodies that bind to independent sites on the antigen or alternatively, affinity-purified antibodies. See pages 555, 559, 561, and 578-579. More particularly, a fluid sample is applied to a solid phase upon which a first antibody is bound, allowing the antigen to bind to the antibody. Next, a second labeled antibody is bound to the antigen and the label is detected, allowing the antigen to be quantified. See pages 578-580.

Harlow & Lane therefore teach a method for measuring the level of an antigen in a fluid sample , in which the measuring uses a monoclonal or polyclonal antibody that is specific to the antigen being determined.

Harlow & Lane is generic with respect to the antigen being determined, and does not teach the antigen mid-proAM (SEQ ID NO:3).

Kennedy et al. teach that preproadrenomedullin is a 185-amino acid molecule that is processed into adrenomedullin as well as other biologically active peptides, including the peptide corresponding to amino acids 45-92 of preproadrenomedullin. See page 832, left column.

Kennedy et al. further teach that there clearly exists a need for defining the specific role of adrenomedullin and its related peptides in normal and pathological states (page 832, right column).

The teachings of Kennedy et al. indicate that the peptide corresponding to amino acids 45-92 of preproadrenomedullin (i.e., mid-proAM or SEQ ID NO:3) was known in the art to exist and to be a biologically active peptide that is related to adrenomedullin. Kennedy et al. also call for studies to define the specific role of this peptide.

It would have been obvious to one of ordinary skill in the art to employ the assay methods of Harlow & Lane in order to detect and quantitate mid-proAM in the course of carrying out studies to define the specific role of this peptide, as suggested by Kennedy et al. For example, as Kennedy et al. discuss the possible role of adrenomedullin and its related peptides (including mid-proAM) in normal and pathological states, it would have been obvious to detect and quantify these molecules in samples taken from normal individuals and individuals known to have disease in order to investigate the possible role of mid-proAM in disease.

With respect to claim 22, Kennedy et al. teaches that adrenomedullin circulates in plasma (see page 832). When taken together with the teaching that both mid-proAM and adrenomedullin are processed from the same larger precursor molecule (preproadrenomedullin), it would have been obvious to also conduct the methods of Harlow & Lane and Kennedy et al. on plasma samples since mid-proAM would also be likely to be found in plasma.

With respect to claim 26, it is noted that the preamble of the claim refers to diagnosis, prognosis or therapy-accompanying monitoring. The normal purpose of a claim preamble is to recite the purpose or intended use of the claimed invention. Such statements merely define the context in which the invention operates and usually will not limit the scope of the claim (MPEP 2111.02 and DeGeorge v. Bernier, Fed. Cir. 1985, 226 USPQ 758, 761 n.3). In the instant case, the body of the claim only sets forth a step of measuring the level of mid-proAM, which is suggested by the teachings of Harlow & Lane and Kennedy et al. as discussed above. Because the claim does not include any active method steps in which disease is actually diagnosed, for example, the reference to such clinical goals in the preamble may be reasonably interpreted as being directed only to a possible intended use or downstream use of the claimed method.

For these reasons, the teachings of Harlow & Lane and Kennedy et al. read on the claim since the preamble does not clearly add any additional limitations to the claim. See also MPEP 2111.04.

Similar issues arise in regards to claims 16, 24, 27-29, and 39, which do not clearly require any steps in which diagnosis or prognosis is actually determined.

Regarding claim 5, in light of the teachings of Harlow & Lane discussed in detail above, it would have been obvious to arrive at the claimed invention by raising antibodies against C-

terminal sequences of SEQ ID NO:3, since amino acids 60-94 correspond to the C-terminus of SEQ ID NO:3. It would have been obvious to do this according to routine laboratory procedures which suggest C-terminal sequences as being likely to produce antibodies that recognize the native protein.

Regarding claim 8, Harlow & Lane also teach that pure antigens or bacterially-expressed proteins can be used to raise antibodies as detailed above. Therefore, it would have been further obvious to arrive at the claimed invention by produce the antibodies for the sandwich immunoassays using either SEQ ID NO:3, either as pure antigen or in bacterially-expressed form. Since SEQ ID NO:3 *per se* "comprises" amino acids 68-86 and 83-92 of pre-proAM, antibodies raised against full-length SEQ ID NO:3 (either as pure antigen or as a bacterially-expressed protein) would read on the recited process.

Motivation to do this comes from the teachings of Harlow & Lane that it is routine in the art to raise antibodies against pure antigen, synthetic peptides, or bacterially expressed proteins.

35. Claims 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harlow & Lane in view of Kennedy et al. as applied to claim 3 above, and further in view of Mathis et al. ("Probing Molecular Interactions with Homogeneous Techniques Based on Rare Earth Cryptates and Fluorescence Energy Transfer" Clin. Chem. 41/9, 1391-1397 (1995)).

Harlow & Lane teach sandwich immunoassays that employ labeled antibodies, but fail to specifically teach that the labeling system is based on fluorescence or chemiluminescence extinction as claimed, or in particular a system that comprises cryptate emission in combination with a fluorescent or chemiluminescent dye.

Mathis et al. teach homogeneous immunoassay methods based on the use of rare earth cryptates as fluorescent labels (the abstract and page 1392). Such immunoassays involve two monoclonal antibodies raised against the antigen, which are labeled respectively with Eu^{3+} cryptate (rare earth cryptate) and with allophycocyanin (cyanine type fluorescent dye). See page 1392 and Figure 1 in particular.

Mathis et al. further teach that such homogeneous fluoroassays are free from media interactions, allowing for development of assays that involve only a minimal perturbation of equilibrium or steric environment (page 1395, "Discussion" to page 1396, left column).

Therefore, it would have been further obvious to one of ordinary skill in the art to modify the solid phase sandwich immunoassay of Harlow & Lane and Kennedy et al. so as to use the rare earth cryptate labeling system of Mathis et al. (which produce fluorescence emission) In particular, it would have been obvious to label one of the antibodies in the sandwich assay of Harlow & Lane with Eu^{3+} cryptate and the other with allophycocyanin as taught by Mathis et al. in order to detect SEQ ID NO:3 in a homogeneous sandwich assay. Put another way, it would have been obvious to use the homogeneous sandwich fluoroassay of Mathis et al. in order to detect and quantitate SEQ ID NO:3 as taught by Harlow & Lane and Kennedy et al.

One would be motivated to do this in light of the teachings of Mathis et al. that the use of rare earth cryptates as fluorescent labels in immunoassays allows for homogeneous assays (i.e., no separation steps). Therefore, one would be motivated to perform a sandwich immunoassay for SEQ ID NO:3 using the labels of Mathis et al. so as to eliminate the need for separation or wash steps needed for typical ELISA procedures (such as that of Harlow & Lane). Furthermore, one

would have been motivated to detect SEQ ID NO:3 by the homogeneous fluoroassay of Mathis et al. in order to allow for an assay that is free from media interactions.

One would have had a reasonable expectation of success because Mathis et al. also teaches that labeling of different types of molecules was done with ease (page 1395, "Discussion").

36. Claims 23 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harlow & Lane in view of Kennedy et al. as applied to claims 3 and 35 above, respectively, and further in view of Bergmann et al. (WO 00/22439).

37. Claims 34, 54, and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harlow & Lane in view of Kennedy et al.

Harlow & and Kennedy et al. are as discussed in detail above, which suggest a method of detecting mid-proAM by immunoassay. However, the references fail to specifically teach a method in which mid-proAM is detected in a sample from a patient with *sepsis*.

Bergmann et al. teach determining pro-adrenomedullin in the serum of normal subjects and those suffering from sepsis; elevated levels were seen in the sepsis patients (see pages 17-19, section D.2; Figure 7 and the accompanying legend on page 8; and Table 3). It is noted that although the Bergmann et al. reference is in German, a translation of the document is available by way of the U.S. counterpart (US 6,756,483 B1, also of record).

When taken together with the teachings of Bergmann et al. which suggest the involvement of adrenomedullin in sepsis, it would have been obvious to measure the level of mid-proAM in serum of patients with sepsis and in normal subjects in the same manner

illustrated by Bergmann et al. for pro-adrenomedullin. Motivation to combine the reference teachings in this manner comes from the teachings of Kennedy, who explicitly call for studies to define the specific role of adrenomedullin and its related peptides, including mid-proAM, in normal and pathological states. As such, it would have been obvious to employ the assay methods of Harlow & Lane and Kennedy et al. in order to measure mid-proAM in the serum of sepsis patients and in healthy controls, in order to define the specific role of this peptide in the pathological state of sepsis.

When the claims are given their broadest reasonable interpretation, the recitation that the measured level "has an order of magnitude of 12 times said level in a healthy person" may be taken as a statement regarding the fundamental physiological properties of mid-proAM in relation to sepsis. In other words, it is presumed absent evidence to the contrary that when measuring mid-proAM in patients with sepsis, levels would necessarily be 12 times those measured in healthy individuals. Consequently, although the reference are silent as to this precise level of increase, the evidence of record suggests that the recited feature would necessarily follow when measuring mid-proAM in patients with sepsis according to the methods of Harlow & Lane and Kennedy et al.

Double Patenting

38. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re*

Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The following are provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

39. Claims 1, 15-16, 19-29, and 31-70 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of copending Application No. 11/937061. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '061 application also claims a method of determining the level of pro-adrenomedullin or partial peptides or fragments thereof for *in vitro* diagnosis of patients post-myocardial infarction (see claim 1). The peptide fragment may be MR-proADM (see claim 2), which is the same peptide as the instantly recited SEQ ID NO:3 (see the specification of the '061 application at [006], which defines "MR-proADM as the peptide comprising amino acids 45-92 of preproADM). The '061 application also claims that additional markers can also be determined (i.e., multi-parameter determination). See claims 4-15.

40. Claims 1, 15-16, 19-29, and 31-70 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of copending

Application No. 12/374,757. Although the conflicting claims are not identical, they are not patentably distinct from each other because Application No. 12/374,757 also claims a method in which the concentration of mid-proAM ("MR-proADM") is determined by sandwich immunoassay (see especially claims 1-4).

With respect to claims 27-29, which recite diagnosis of a disease other than sepsis, it is noted that the instant specification defines "diagnosis" so as to encompass monitoring of treatment (see [002] of the published application), which is the same purpose for which the method of the copending application is performed (see preamble of claim 1). In particular, Application No. 12/374,757 teaches a method for assessing changes in concentration due to treatment for *cardiac insufficiency.*

41. Claims 1, 15-16, 19-29, and 31-70 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of copending Application No. 12/305,088. Although the conflicting claims are not identical, they are not patentably distinct from each other because copending Application No. 12/305,088 also claims a method of determining the concentration of a midregional proADM fragment (MR-proADM) which comprises the amino acids 45-92 of pre-proadrenomedullin (i.e., mid-proAM). See in particular claims 1, 5, and 8. Biological fluid samples assayed may be blood, serum or plasma (claim 6). The method can be conducted using sandwich-type immunoassays (claim 10).

With respect to claims 27-29, Application No. 12/305,088 claims a method for detection or prognosis of neurodegenerative diseases.

42. Claims 2-9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over any one of: claims 1-17 of copending Application No. 11/937061; claims 1-13 of copending Application No. 12/305,088; or over claims 1-13 of copending Application No. 12/374,757 in view of Harlow & Lane.

The '088 and '757 applications recite a sandwich immunoassay (claims 4), but do not specifically mention that the assay uses a labeled analyte-specific antibody. The copending applications also fail to specifically recite that the antibodies for the sandwich immunoassay bind to a region on mid-proAM that extends from amino acids 60-94 of pre-proAM, or that the antibodies are obtained by immunization with the synthetic peptides recited in claim 8.

Harlow & Lane is as discussed above, which teaches laboratory procedures involving antibodies, including immunoassays. For example, the reference teaches that one of the most useful immunoassays is the two-antibody sandwich technique, which can be used to determine antigen concentration in a quick and accurate manner (pages 578-579). Such sandwich immunoassays require two antibodies that bind to non-overlapping epitopes on the antigen; either two monoclonal antibodies or one batch of affinity-purified polyclonal antibodies can be used (ibid). The first antibody is bound to a solid phase, while the second antibody is labeled (see diagram on the bottom of page 578, and page 579).

Harlow & Lane also teach that it is routine in the art to use synthetic peptides as immunogens in order to raise antibodies, and suggest carboxy-terminal sequences for designing such peptides since they are likely to be immunogenic and because a surprisingly high percentage of antibodies raised using carboxy-terminal sequences will recognize the native protein. See pages 53, 60-61, and 72-76.

Regarding claims 2-3 and 9, it would have been obvious to arrive at the claimed invention by employing the sandwich immunoassay format of Harlow & Lane to detect MR-proADM in the methods of the copending applications. One would also be motivated to do this in light of the teachings of Harlow & Lane that sandwich immunoassays are one of the most useful immunoassays, being quick and accurate.

It would have been further obvious to select either monoclonal or affinity-purified polyclonal antibodies for such a sandwich immunoassay (as in claims 6-7) since Harlow & Lane taught that both of these produce excellent signal strength and specificity.

Regarding claim 5, in light of the teachings of Harlow & Lane discussed in detail above, it would have been obvious to arrive at the claimed invention by raising antibodies against C-terminal sequences of SEQ ID NO:3, since amino acids 60-94 correspond to the C-terminus of SEQ ID NO:3. It would have been obvious to do this according to routine laboratory procedures which suggest C-terminal sequences as being likely to produce antibodies that recognize the native protein.

Regarding claim 8, Harlow & Lane also teach that pure antigens or bacterially-expressed proteins can be used to raise antibodies as detailed above. Therefore, it would have been further obvious to arrive at the claimed invention by produce the antibodies for the sandwich immunoassays using either SEQ ID NO:3, either as pure antigen or in bacterially-expressed form. Since SEQ ID NO:3 *per se* "comprises" amino acids 68-86 and 83-92 of pre-proAM, antibodies raised against full-length SEQ ID NO:3 (either as pure antigen or as a bacterially-expressed protein) would read on the recited process.

Motivation to do this comes from the teachings of Harlow & Lane that it is routine in the art to raise antibodies against pure antigen, synthetic peptides, or bacterially expressed proteins.

43. Claims 2-3, 6, and 10-11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over any one of: claims 1-17 of copending Application No. 11/937061; 1-13 of copending Application No. 12/305,088; or over claims 1-13 of copending Application No. 12/374,757 in view of Mathis et al. ("Probing Molecular Interactions with Homogeneous Techniques Based on Rare Earth Cryptates and Fluorescence Energy Transfer" Clin. Chem. 41/9, 1391-1397 (1995)).

The '757 and '088 applications recites sandwich immunoassays (claims 4), but do not specifically mention that the assay uses a labeled antibody. The copending applications also fail to recite an immunoassay that involves a labeling system that comprises cryptate emission in combination with a fluorescent or chemiluminescent dye.

Mathis et al. teach homogeneous immunoassay methods based on the use of rare earth cryptates as fluorescent labels (the abstract and page 1392). Such immunoassays involve two monoclonal antibodies raised against the antigen, which are labeled respectively with Eu^{3+} cryptate (rare earth cryptate) and with allophycocyanin (cyanine type fluorescent dye). See page 1392 and Figure 1 in particular.

Mathis et al. further teach that such homogeneous fluoroassays are free from media interactions, allowing for development of assays that involve only a minimal perturbation of equilibrium or steric environment (page 1395, "Discussion" to page 1396, left column).

In light of the teachings of Mathis et al., it would have been obvious to one of ordinary skill in the art to detect pro-adrenomedullin 45-92 (MR-proADM, SEQ ID NO:3) in the methods of the copending applications by the fluoroimmunoassay of Mathis et al. in the method of Bergmann et al. In particular, it would have been obvious to use two monoclonal antibodies against the antigen (i.e., pro-adrenomedullin 45-92) and to label one of the antibodies with Eu^{3+} cryptate (i.e., rare earth cryptate) and the other with allophycocyanin (i.e., fluorescent cyanine-type dye). Put another way, it would have been obvious to use the homogeneous sandwich fluoroassay of Mathis et al. in order to detect MR-proADM in the methods of the '250 or '061 applications. One would be motivated to do this in order to detect pro-adrenomedullin 45-92 in a homogeneous assay, requiring no separation steps. One would also be motivated to use the Mathis et al. fluoroimmunoassay in order to avoid the need to use radioactive labels.

44. Claims 1-9, 15-16, 19-29, and 31-70 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 12/514,194 and Harlow & Lane.

Application No. 12/514,194 also claims a method in which the concentration of mid-proAM ("MR-proADM") is determined (see especially claim 1). However, the copending application does not specifically recite that such a method uses an antibody.

However, in light of the teachings of Harlow & Lane discussed in detail above, it would have been obvious to employ the known two-antibody sandwich immunoassay format since this type of assay was recognized to be the most useful means of detecting and quantitating antigens.

45. Claims 10-11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 12/514,194 and Harlow & Lane as applied to claim 3 above, and further in view of Mathis et al.

The copending application and Harlow & Lane fail to specifically teach that the labeling system is based on fluorescence or chemiluminescence extinction as claimed, or in particular a system that comprises cryptate emission in combination with a fluorescent or chemiluminescent dye.

However, in light of the teachings of Mathis et al. discussed in detail above, it would have been obvious to employ such a labeling system in order to avoid the need for separation or wash steps typically required in a sandwich immunoassay (such as that of Harlow & Lane).

Response to Arguments

46. Applicant's arguments filed 10/7/2009 have been fully considered.

47. With respect to the rejections of claims 27-29 under § 112, 2nd paragraph as being incomplete for omission of essential missing step, Applicant's reply does not apparently include arguments traversing the rejections, which are therefore maintained for reasons of record.

48. With respect to the rejections of claims 27-29 under § 112, 1st paragraph (enablement), Applicant's arguments (Reply, page 5) have been fully considered but are not found persuasive.

Applicant argues that increased amounts of adrenomedullin (ADM) have been correlated in the prior art with a number of diseases. However, the claims at issue do not relate to the use of ADM as a marker but rather to mid-proAM. Applicant has argued that mid-proAM is a "newly

discovered partial peptide [which was] heretofore not known" (see Reply, page 21, last paragraph).

It does not necessarily follow that peptides derived from the same precursor molecule possess the same function. See the instant specification at pages 4-5, where it is discussed how the concentrations of such peptides may be different.

In addition, Qui et al. (of record) teach that it was well known that peptides derived from a common polypeptide precursor through proteolytic cleavage "usually have different biological activities" (see page 1145, left column, last paragraph).

Therefore, it cannot be automatically assumed that mid-proAM would also serve as a disease marker in the same manner that ADM does, simply because it is derived from a common precursor molecule. Rather, the prior art suggests that even such related peptides usually have different functions, such that data establishing a nexus of mid-proAM with disease is necessary.

Moreover, the claims broadly encompass diagnosis or prognosis of any disease. It is not credible that mid-proAM could be used in this manner. It is maintained for reasons of record that the specification fails to teach the skilled artisan how to diagnose or prognose any disease.

49. With respect to the art rejections based upon Bougueleret et al. as maintained above, Applicant argues that the priority document is identical to the instant specification and therefore supports the claims in the same manner (Reply, page 26). However, the rejected claims present new matter not found in either the instant specification or in the priority document, such that they are not entitled to the benefit of the earlier filing date. As such, it is maintained that Bougueleret et al. is prior art.

50. With respect to the provisional obviousness-type double patenting rejections, Applicant acknowledges but does not presently address the rejections (Reply, page 26), which are therefore maintained for reasons of record.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, can be reached at (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine Foster/
Examiner, Art Unit 1641